

to Berk Pharmaceuticals Ltd. for supplies of povidone-iodine; and to Messrs. Allen & Hanburys for supplies of laurolinium acetate.

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## Final Report of a Prospective Study of Children whose Mothers had Rubella in Early Pregnancy

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A controlled prospective inquiry regarding the effects of rubella and other virus infections in pregnancy, beginning early in 1950 and ending in December 1952, and sponsored by the Ministry of Health, was fully reported by Manson, Logan, and Loy (1960). The total number of pregnancies complicated by rubella available for analysis was 578. The controls numbered 5,717. Follow-up of the infants showed that when rubella occurred during the first 16 weeks of pregnancy the incidence of congenital abnormalities in the children was significantly raised. When the infection occurred after the 16th week the incidence of abnormalities in the children of the rubella mothers was no higher than in the controls.

The number of pregnancies complicated by rubella in the first 16 weeks was 279. Of these, 11 ended in abortion and 11 in stillbirth, and 16 children died before 2 years of age, leaving 241 in the original group. A number of medical officers of health continued to send in records of children born in 1953 whose mothers had been notified for rubella before the end of 1952. Since these cases fulfilled the criteria laid down by Logan (1951), a further 18 infants whose mothers had rubella in the first 16 weeks of pregnancy were added to the original group. This gave a final total of 259 children available for assessment at 2 years, by which age it had been anticipated that all major abnormalities would have been diagnosed. This examination is designated No. 1 in Table I.

In order to check the possibility of hitherto unidentified defects, however, full paediatric and otological examination of 57 "early rubella" children and 57 controls living in the London and Middlesex areas was undertaken in 1956–7 by Jackson and Fisch (1958), the children concerned being then between the ages of 3 and 6 years. The results of their inquiry indicated that the proportion of children suffering from significant hearing loss had been underestimated at the original examination. It was therefore considered advisable to extend the inquiry to "early rubella" children living in the rest of the country. Reports for 237 children were received and the results were included in the report of Manson *et al.* (1960). This examination is designated No. 2 in Table I.

Finally, in order to discover how they developed in later childhood a third inquiry was carried out in 1962, when the children were between the ages of 8 and 11 years. The present paper reports the results of this examination, which is designated No. 3 in Table I, in relation to findings of the previous examinations.

\* Ministry of Health.

### The Report Form

The medical officers of health were requested to provide the following particulars: (1) Any abnormality of the eyes: visual acuity right and left, distant and near, without and with spectacles if worn. (2) Any abnormality of the ears: hearing right and left for quiet conversational voice without lip-reading at 3 and 10 ft. (0.9 and 3 m.). Also a full pure-tone audiogram. (3) Condition of the heart as reported by a cardiologist or paediatrician. (4) Intelligence quotient, naming testing scale used. (5) Assessment of the child's emotional development and social behaviour. (6) Any other pathological condition present. (7) Type of school attended.

A total of 227 completed reports were received. Of the remaining 32, one child had emigrated, the parents of five children refused to participate, and 26 were untraced.

Owing to the wide geographical distribution of cases and the large number of medical examiners concerned, it was inevitable that the reports received were not equally informative, but the general standard of recording was high. Assessment of an abnormality as major or minor on the evidence available sometimes required much thought, and final classification is necessarily the result of my personal judgment. For this reason, and because there were no controls, it proved difficult to submit the very varied information collected to any sophisticated statistical analysis. It has therefore been decided to present it in tabulated form.

The final outcome of this prospective study has confirmed the findings of previous, mainly retrospective, inquiries regarding the special vulnerability to rubella infection of the eyes, ears, and heart of the developing foetus during the first 16 weeks of pregnancy. It does not, however, bear out the very pessimistic evaluations of attendant risks which have sometimes been offered on the basis of retrospective studies. Major abnormalities were present in 33 (15%) children, 20 of whom had more than one abnormality. Minor abnormalities were noted in 37 (16%) children, of whom 9 had another abnormality. In both groups, particularly the latter, it is probable that some of the children included were suffering from conditions unrelated to the rubella infection, although in compiling the tables only those children whose abnormalities were considered from the information available to be certainly or possibly due to rubella have been included. Hence 11 children showing single abnormalities which were either known or thought unlikely to be connected with the maternal rubella infection have been omitted from the tables—that is, two cases of myopia devel-

oping in middle childhood, two cases of hearing loss associated with active otitis media, six cases of uncomplicated educational subnormality, and one case of paralytic poliomyelitis.

Table I summarizes according to the pregnancy week of rubella infection the number of children at risk, the number showing abnormalities, and the number and nature of the abnormalities occurring in each affected child.

**Major Abnormalities.**—The number and associations according to week of infection are shown in Table II.

**Minor Abnormalities.**—The associations and number of cases are shown in Table III.

### Eye Defects

Cataract was noted in seven cases and never as a single abnormality: six of these children had congenital lesions of the heart and five of them were also deaf; the remaining child had a paralytic squint. The cataract was bilateral in three cases and unilateral in four. All seven were associated with infection in the first to ninth week. Visual acuity was recorded for all but 4 of the 227 children: two of these were blind and two were noted as having been successfully operated upon—one for cataract and the other for squint. Squint was noted in seven cases, five of them for the first time at the third examination. Defective vision was noted in eight cases for the first time at the third examination, and unilateral amblyopia was noted three times—one in association with another disability. Some of these visual defects may have been due to causes other than maternal rubella. In the absence of any note to the contrary, it is not possible to differentiate. Nevertheless,

the need for continual reassessment before and after school entrance is clearly indicated.

### Ear Defects

The inquiry has shown up very clearly the importance of rubella in early pregnancy as a cause of congenital deafness.

TABLE II

No. of Abnormalities	Nature	Week
5	Bilateral cataract, deafness, congenital heart, spasticity, mental defect	1
	Squint, deafness, congenital heart, undescended testicle	7
4	Bilateral cataract, deafness, congenital heart, spasticity	9
	Unilateral cataract, deafness, congenital heart E.S.N.	9
	Defective vision, deafness, E.S.N., undescended testicles	15
3	Bilateral cataract, congenital heart, emotional maladjustment	5
	Defective vision, deafness, heart murmur	6
	Unilateral cataract, deafness, congenital heart	8
	Defective vision, deafness, spasticity	8
	Deafness, heart murmur, asthma	11
	Deafness, congenital heart, aphasia	12
2	Unilateral cataract, paralytic squint	4
	Pyloric stenosis, asthma	8
	Deafness, congenital heart (2 cases)	5, 8
	Squint, deafness (2 cases)	5, 12
	Unilateral cataract, heart murmur	9
	Deafness, migraine	12
	Unilateral amblyopia, asthma	15
Single	Deafness (8 cases)	4, 5, 7, 8, 10, 10, 10, 12
	Congenital heart (3 cases)	3, 7, 12
	Duodenal stenosis	9
	Pyloric stenosis	10

TABLE I

Week	No. of Children	No. with Abnormalities	No. of Abnormalities per Child	Nature of Abnormalities and When First Noted
1	11	Major 1 Minor 1	5 2	Cataracts 1; deafness 2; C. heart 1; subnormality 1; motor handicap 3 Malformed right ear 1, with unilateral deafness 3; undescended testicles 3
2	6	Major 0 Minor 1	— 1	Defective vision 3
3	8	Major 1 Minor 2	1 1 1	Congenital heart 1 Mild deafness right and left 2. Heart murmur 3
4	16	Major 2 Minor 4	2 1 2 1 1 1	Cataract left and right squint 1. Severe deafness 2 Mild deafness right and left and heart murmur 3. Deafness right and left 3. Heart murmur 3.
5	14	Major 4 Minor 1	3 2 2 1 2	Cataracts 1; C. heart 3; maladjusted 3. Squint 3; deafness 2. Deafness 2; C. heart 2. Deafness 1 Deafness right and left 3; heart murmur 3
6	5	Major 1 Minor 3	3 2 2 1	D. vision 3; deafness 2; heart murmur 3 Squint 3; heart murmur 3. Deafness right and left 3; heart murmur 3. Squint 3
7	11	Major 3 Minor 2	4 1 1 1 1	Squint with d. vision 1; deafness 3; C. heart 1; undescended testicle 3. C. heart 1. Deafness 1 Minor C. heart 1. Heart murmur 3
8	22	Major 5 Minor 3	3 3 2 2 1 2 2 1	Cataract R. 1; deafness 2; C. heart 1. D. vision 3; deafness 1; spasticity 1. Deafness 1; C. heart 1. Pyloric stenosis 1; asthma 1. Deafness 2 D. vision 3; deafness right and left 3. Deafness 3; squint 3. Unilateral deafness 3
9	14	Major 4 Minor —	4 4 2 1	Cataract right and left 1; deafness 1; C. heart 1; spastic 1. Cataract left 1; deafness right and left; 3 C. heart 1; E.S.N. 3. Cataract left 1; C. heart 1. Duodenal stenosis 1
10	16	Major 4 Minor 2	1 1 1 1 1 1	Deafness 1. Deafness 1. Deafness 1. Pyloric stenosis 1 Heart murmur 3. Deafness right and left 3
11	17	Major 1 Minor 0	3	Deafness 3; heart murmur 3; asthma 3
12	20	Major 5 Minor 7	3 2 2 1 1 1 1 1 1 1 1 1	Deafness 2; C. heart 3; aphasia 2. Squint with d. vision 3; deafness 1. Deafness 1; migraine 2. Deafness 2. C. heart 3 Unilateral amblyopia L. 3. Unilateral deafness 2. Unilateral deafness 2. Unilateral deafness 3. Deafness 3. Heart murmur 3. Heart murmur 3
13	16	Major — Minor 1	— 1	Unilateral deafness 3
14	15	Major 0 Minor 3	— 2 1 1	Unilateral deafness 3; undescended testicles 3. D. vision 3. Deafness 3
15	24	Major 2 Minor 6	4 2 2 1 1 1 1 1	D. vision 3; deafness 1; E.S.N. 1; undescended testicles 3. Unilateral amblyopia 3; asthma 3 Deafness 3; heart murmur 3. Unilateral amblyopia 3. Deafness 2. Deafness 2. Heart murmur 3. Heart murmur 3
16	12	Major — Minor 1	— 1	Heart murmur 3
Totals	227	Major 33 Minor 37	Major 15% Minor 16%	

The figures 1, 2 and 3 in the last column refer to the number of the examination (see text).

TABLE III

No. of Abnormalities	Nature	No. of Cases
2	Malformation of right ear with unilateral deafness, undescended testicles .. ..	1
	Bilateral deafness, heart murmur .. ..	4
	Squint, heart murmur .. ..	1
	Squint, bilateral deafness .. ..	1
	Defective vision, bilateral deafness .. ..	1
	Unilateral deafness, undescended testicle ..	1
Single	Squint .. ..	1
	Unilateral amblyopia .. ..	2
	Defective vision .. ..	2
	Bilateral deafness .. ..	7
	Unilateral deafness .. ..	5
	Congenital heart .. ..	1
	Heart murmur .. ..	10

The cases were associated with infection from the first to the fifteenth week. Pure-tone audiograms as well as the results of clinical voice tests—that is, quiet conversational voice without lip-reading at 3 and 10 ft. (0.9 and 3 m.) right and left) were available for 179 (79%) children and the results of clinical tests alone were available for 46. The remaining two were attending schools for the deaf, and were incapable of responding to either test. In assessing the audiograms for summary in the tables it was necessary to adopt some standard of classification. It was finally decided that hearing loss over 20 decibels must be shown for at least two adjacent frequencies and the degree of deafness was evaluated as follows: Mild deafness=loss of 20–45 db., moderate deafness=loss of 45–70 db., and severe deafness=loss of 70+ db. On these standards, 43 (19%) children had a significant hearing loss: 23 (10%) had severe or moderate bilateral deafness necessitating some form of special education; 14 had mild bilateral loss; and 6 had unilateral deafness which was moderate or severe. These last 20 (9%) children were able to attend ordinary school, some of them wearing hearing-aids, and others receiving speech therapy or other forms of special help.

No fewer than 17 cases with significant degrees of deafness were noted for the first time at the third examination, and in 10 of these the hearing loss was bilateral. Five of the 10 showed a serious loss, three of these five children had additional abnormalities, which had been duly recorded at previous examinations. The need for thorough periodic investigation of the hearing in all children at risk, whether or not there is another presenting abnormality, is obvious. It is, of course, possible that some of these late discoveries were children whose deafness was not due to rubella, but there was no suggestion of other causation in the reports.

Of the 43 children with significant hearing loss 36 audiograms were available. Of the other seven, two were in schools for the deaf, four were in ordinary schools wearing hearing-aids, and one was the multi-handicapped child in hospital. Of the 36 available audiograms, 26 showed a flat loss over the whole speech range and 10 showed curves sloping from left to right—that is, high-tone deafness—thus confirming the original observations of Fisch (1955) regarding the audiometric patterns commonly associated with rubella deafness.

### Heart Defects

The amount of information available regarding cardiac abnormalities was particularly satisfactory. The report of a cardiologist or consultant paediatrician was available for all except about a dozen children whose attendance at hospital or special clinic had been too difficult to arrange. In these cases the school medical officer had examined the child. Fourteen cases were definitely diagnosed as congenital lesions, the weeks of infection being from 1 to 12. In 10 cases the cardiac lesion was associated with another abnormality; in four it was the sole abnormality noted. Eighteen heart murmurs described as “innocent” or “of no significance” were recorded (16 of them for the first time at the third examination), but it is noteworthy

that nine of these (seven of the 16) were associated with another abnormality.

### Other Conditions

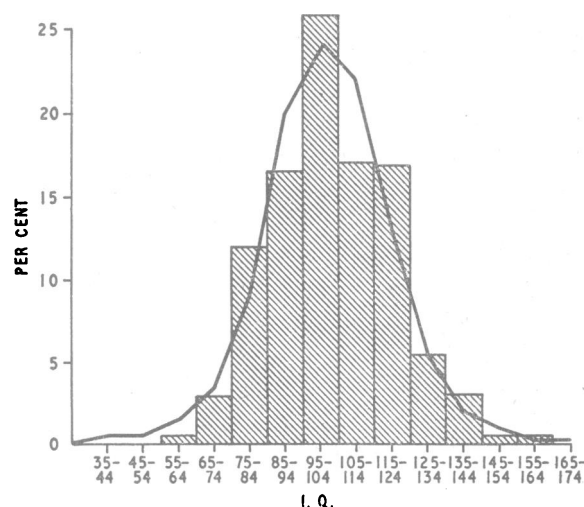
Asthma was noted three times and migraine once, all in association with another abnormality. Four cases of undescended testicles were noted, also in association with another abnormality. Spasticity of the limbs was noted in three cases, and all three children had other handicaps. Two cases of pyloric stenosis and one of duodenal stenosis, which were reported at previous examinations as having been successfully operated upon during infancy, were noted to be doing well.

### Social Adjustment

It has been suggested that rubella children often show emotional instability and difficult behaviour, but although the information was specifically requested there was little supportive evidence in the reports. Twelve children were variously noted as “shy,” “immature,” “lacking in concentration,” or “liable to outbursts of temper,” but only one, a blind child, was reported as “psychologically difficult.”

### Intelligence

Intelligence quotients were available for 191 (84%) children and teachers' assessments for the remaining 36. The testing scales were Terman-Merrill (174), WISC (14), and other standard scales (3). In the circumstances it was thought permissible to combine these to plot a curve of distribution, which is shown in the Chart. It proved to be strikingly normal.



Distribution of I.Q.s of rubella group with superimposed curve of T.M. standardization group.

The mean I.Q. was 106.8, with a range of 63 to 160. The teachers' estimates for the remaining 36 were as follows: 27 average, 1 above average, 6 below average, 1 borderline, and 1 mentally handicapped. The number of children concerned, range of I.Q., and teachers' assessment according to the week of maternal rubella are given in Table IV. It is worthy of note that of the 37 children with I.Q.s under 85, or designated “below average,” 13 had a significant hearing loss, which raises the question to what extent their lowered performance on tests was due to their sensory disability. Although it is convenient for statistical purposes to record the results of intelligence tests in terms of a numerical I.Q., it needs to be kept in mind that the results of testing (British) handicapped children with intelligence scales standardized on a normal (North American) child population can only be justified clinically by using some such form of words as “the I.Q. is not less than. . .” It can

safely be said that this inquiry has produced no evidence that mental subnormality is a common sequel of early maternal rubella.

TABLE IV.—*Intelligence. Distribution According to Time of Rubella Infection*

Week	No. of Cases	I.Q.			Additional Assessments
		Given	Mean	Range	
1	11	9	102	88–141	1 below average, 1 severely subnormal
2	6	4	116	83–131	2 average
3	8	8	110	96–139	
4	16	11	103	80–128	5 average
5	14	13	101	71–150	1 average
6	5	5	112	80–130	
7	11	10	103	80–142	1 average
8	22	19	108	84–134	2 average, 1 borderline
9	14	13	95	63–110	1 average
10	16	11	107	82–160	4 average, 1 below average
11	17	17	107	83–140	
12	20	15	107	70–143	2 average, 3 below average
13	16	14	110	80–133	1 above average, 1 average
14	15	14	103	83–134	1 average
15	24	18	109	70–145	5 average, 1 below average
16	12	10	116	93–143	2 average

I.Q. mean for 191 cases = 106.8.

### Education

The educational placement of the 227 children is shown in Table V.

TABLE V

Ordinary school .. .. .	199
Ordinary school with special help ..	7
Special schools or classes, etc.:	
For deaf or partially deaf .. .. .	15
For partially sighted .. .. .	1
For speech defectives .. .. .	1
For E.S.N. .. .. .	1
Home tuition .. .. .	1
Hospital for mentally subnormal ..	1
[P.H. school—paralytic polio (not rubella)]	1

Thus 206 (92%) of the children were attending ordinary schools. Of these 7 (3%) are noted as having special provision such as hearing-aids, speech therapy, remedial teaching, etc. Twenty children were attending special schools or classes, including the child whose handicap was the result of paralytic poliomyelitis. The majority of those in special schools were severely deaf. The child receiving home tuition was blind and maladjusted. He had also been operated upon for a congenital heart lesion, a residual murmur being present. The child who was in a hospital for the mentally subnormal had multiple handicaps.

### Birth Weights

Birth rates were available for 226 of the 227 children. The missing record referred to a (fifth week) child with multiple major abnormalities. The figures (Table VI) show a suggestive trend.

TABLE VI.—*Birth Weight of 226 Children*

Children	Mean		Range	
	lb. oz.	g.	lb. oz.	g.
Normal (157) .. .. .	7 2	3,230	4 10–10 2	2,100–4,590
With minor abnormalities (37) ..	6 10	3,005	3 13–10 6	1,730–4,705
With major abnormalities (32*) ..	6 4½	2,850	3 13–8 8	1,730–3,855
With multiple major abnormalities (19) .. .. .	5 14	2,665	4 6–8 4	1,985–3,740

\* These 32 cases include the 19 with multiple major abnormalities.

### Missing Cases

In order to complete this record the previous reports of the missing 32 children were scrutinized. Four of them had abnormalities associated with maternal rubella in the first, eighth and eleventh weeks of pregnancy as follows:

Week 1: Severe unilateral deafness noted at second examination.

Week 8: Congenital heart noted at first examination; and at the second examination reported as having had a successful operation at 2½ years.

Week 8: Unilateral deafness noted at second examination.

Week 11: Squint, severe deafness, talipes, and mental subnormality noted at first examination; no record of any second examination.

### Seasonal Distribution

It has often been suggested that a larger proportion of handicapped children are born in the months of winter and early spring than in the summer. The months of birth of the 259 early rubella children, with and without abnormalities, are given in Table VII.

TABLE VII.—*Months of Birth for Whole Series of 259 Early Rubella Children With and Without Defects*

Month	Normal	Abnormal	Total
January .. .. .	21	15	36
February .. .. .	18	3	21
March .. .. .	6	4	10
April .. .. .	5	1	6
May .. .. .	1	1	2
June .. .. .	2	1	3
July .. .. .	4	2	6
August .. .. .	6	5	11
September .. .. .	21	6	27
October .. .. .	34	6	40
November .. .. .	35	18	53
December .. .. .	32	12	44
Total .. .. .	185	74	259

Although the larger number of "early rubella" children were born in the months October to February inclusive, reflecting the usual springtime incidence of rubella epidemics, there was no significant difference in the proportion of handicapped and non-handicapped children born at any season of the year.

### Summary

A controlled prospective inquiry regarding mothers who had rubella during the first 16 weeks of pregnancy was begun during 1950–2.

Three follow-up medical examinations of the children resulting from these pregnancies were carried out, the first at 2 years (259 children), the second between 3 and 6 years (237 children), and the third between 8 and 11 years (227 children).

The results of the first two examinations were published by Manson, Logan, and Loy (1960).

This paper reports the final outcome of the inquiry, with special reference to the findings of the three examinations.

Major abnormalities, mainly of the eye, ear, and heart, occurred in 15% of the children, 8% having more than one abnormality. Minor abnormalities were present in a further 16%, 4% having more than one abnormality. These are outside estimates, as it is possible that some of the abnormalities discovered were due to causes other than maternal rubella.

The distribution of intelligence among the children was normal.

The need for long-term follow-up and periodic full reassessment of children known to be at risk from maternal rubella during the first 16 weeks of pregnancy was clearly demonstrated.

This inquiry would not have been possible without the generous help of medical officers of health throughout Britain. Dr. M. A. Heasman, of the Ministry of Health's Medical Statistics Section, kindly prepared the graph for the Chart.

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